Pharmaceutical
Research

PARKE-DAVIS

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

1664 '99 SEP -7 A8:32

RE: Docket 99N-0193: "Supplements and Other Changes to an Approved Application", Proposed Rule [64FR34608].

Dear Sir/Madam:

This letter is in reference to the proposed revisions to 21CFR 314.70 that were published in the *Federal Register*, **64**, 34608 (June 28, 1999), Docket 99N-0193.

The US Food and Drug Administration's (Agency) proposal to collapse separate sets of regulations for drug substances and drug products into a common set of regulations based upon the scientific impact of the respective change is reasonable and laudable. However, as presented at the August 19, 1999 FDA Public Meeting on this topic, we concur with the PhRMA and PDA assessments that the proposed changes to the regulations do not meet the full Congressional intent of FDAMA. While there is little or no reduction in actual reporting requirements, it appears there is an overall increase in the number of changes that may now be classified as Prior Approval Supplements.

Specifically, we have the following general concerns regarding the proposed approach:

- This approach is risky in that a number of relevant guidance documents required to support the new regulations are not yet implemented (i.e. BACPAC-I or -II, Stability, etc.) let alone the guidance document "Changes to an Approved NDA or ANDA". As such, it is recommended that a finite period be established in which these guidance documents are completed and issued;
- The subject draft document seeks to extend the authority of the FDA in a number of areas (i.e. compliance with United States Pharmacopoeia [USP] monographs) and increase the regulatory burden on the pharmaceutical industry. This seems at odds with the intent of the November 21, 1997 Food and Drug Administration Modernization Act (FADAMA); and

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- The proliferation of yet another interpretation of the term "validate" can only contribute to confusion in this area, especially regarding ICH global harmonization activities involving mutual recognition as well as the quality section of the Common Technical Dossier (ICH M4). Much more could be done throughout the revised 21CFR314.70 sections to substitute more appropriate terms (i.e. assessment, evaluate, etc) than is currently done. There are serious questions as to which definition of the term "validate" apply within the proposed regulations and guidance documents let alone specific US and EU filing requirements, cGMP requirements not withstanding.

We appreciate the opportunity to comment on the proposed changes to 21CFR314.70 and our specific comments/concerns regarding the various sections of the proposed regulations are summarized below.

Sincerely,

Richard B. Phillips, Ph.D.
Director, Worldwide Regulatory Affairs (CM&C)

Proposed (*draft*) 21CFR314.70

§314.3

While it is recognized that the term "validate the effect of the change" arises directly from Section 506A of The Act as revised, additional clarification of its intent relative to various other meanings associated with the term "validate" and cGMP and EU filing requirements should be provided. Please refer to our comments on §314.70(d)(3)(i).

§314.70(a)(4)

Many labeling changes are minor and prompt revision of associated promotional labeling and/or advertising is not warranted [i.e. §314.70(d)(2)(x) and (xi)]. Recommend revising this section from ". . . in accordance with this section" to . . in accordance with paragraphs (b) and (c) of this section."

§314.70(a)(6)

There should be ample space in the cover letter of a supplement to list the changes that are being effected for a CM&C specific supplement. This also serves to ensure that both the applicant and the Agency are clear on what is actually being approved in the supplement and avoid ambiguity later.

However, to include all of the CM&C changes that are being reported in the cover letter of an annual report (AR) is excessive. The current guidance document regarding the CM&C information of an Annual Report already requires this information be included in Sub-section I of the CM&C section. Recommend deletion of the requirement for annual reports.

§314.70(b)(2)(i)

Please refer to our comments on §314.70(d)(2)(i). As the innovator of the active pharmaceutical ingredient, the pharmaceutical industry relies heavily on the USP compendia to assure that the specifications and methods for inactive ingredients are appropriate. The linkage of this section with that of §314.70(d)(2)(i) may delay

industry's ability to introduce changes required by law (comply with current USP) and/or implement general product improvements.

§314.70(b)(2)(iii)

While "any change" made to the process for a sterile drug product "may affect" the products sterility assurance, this leaves the "requirement" open-ended and ill defined. Recommend that the focus of this section be limited to "changes that have the potential to decrease *or significantly impact* the sterility assurance level" of the product in order to differentiate minor vs major filing requirements.

§314.70(b)(3)(viii) and (c)(3)(iii)

The proposed requirement to include listings and/or cross references to relevant company SOPs is excessive. Many of these SOPs are specific to cGMPs or more extensive for company reasons than required to be submitted for informative purposes only (i.e. general sampling plan, etc) to NDAs. In view of the new §314.70(e) protocol section and the detail found in other guidance documents (i.e. container closure), this constitutes an increase in regulatory burden. Review of relevant cGMP SOPs should remain the responsibility of the FDA field office.

§314.70(c)(2)(i)

In order to avoid misinterpretation, recommend revising this section from "... a change in the container closure system that does not affect the quality . . . " to that of ". . . a *significant* change in the container closure system that does not *adversely* affect the quality . . .".

§314.70(d)(2)(i)

The proposed requirement constitutes an extension of the authority of the FDA with regard to the official compendia of the United States (i.e. USP), which is recognized in Section 501.[351] of The Act as representing the official specification requirements for pharmaceuticals. The additional requirement that the specification for a listed drug "... is consistent with FDA requirements and provides *increased* assurance that the drug will have the characteristics ... that it is purported to have" is excessive. Recommend retaining wording in the current 21CFR314.70(d)(1) without further qualification.

While guidance on establishment of specifications is found in the various ICH Quality documents, the actual "requirements" are often subject to individual reviewer assessment. Therefore, the open review process established by the USP allows for the establishment of reasonable product monographs, which should also be open to FDA participation.

§314.70(d)(2) (x) & (xi)

It is not evident why there is a need to distinguish "natural protein product, a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonal antibody" from other products. These products should be regulated the same way as conventional products. As such, recommend 21CFR §314.70(d)(2)(x) & (xi) be deleted. Should it be deemed that this differentiation is required, we recommend that the specific details be specified in a respective Guidance to Industry document.

§ 314.70(d)(3)(i)

The requirement that the holder include a statement that the changes made in accordance with §314.7(d)(2) and reported in the annual report "have been validated" is excessive. As written, the term "validated" appears to be cGMP related as it applies to "released" or marketed product. In addition, the term is used in a different context from the defined as "validate the effect of the change". If it is still required that some assurance be given

that an assessment of the change was performed, it is recommended that the statement be revised to " . . . that the effects of the change have been *assessed*".

Certainly, if all of the changes reported in the Annual Report were limited to labeling, there would be no relevance of a statement concerning the "validation" of the labeling changes?

§314.70(d)(3)(iii)

Again, inclusion of cross-references to validation protocols and/or SOPs is excessive and represents an increase in the amount of information currently submitted to an NDA. In addition, it is not clear if the protocols referred to herein are internal company protocols/SOPs or those described in §314.70(e) on protocols. Recommend either deletion of this requirement if specific for internal company protocols or further clarification if specific to §314.70(e) based protocols.

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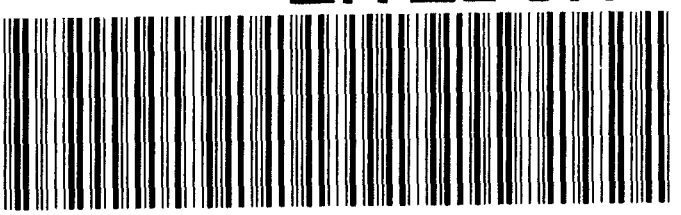

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